Review Article

# Gene Mining for Management of Psychological and Neurodevelopmental Disorders- A Review

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## ABSTRACT

Genetic studies could act as surplus tool in testifying psychological disorders revealing concrete details about diseases. Application of omics-data could assist in classification of neuro-developmental disorders. In this study PCR-based DNA markers were emphasized due to low cost, affordability and high reproducibility. 52 genes were identified including their molecular ontogeny with detection of mono/oligo/polygenic control of diseases. The mono or oligogenic diseases could be controlled easily. The distinct candidate gene approach in tracing of neurodevelopmental disorder is rare. The prevalence of pleiotropic control mechanism of genes in majority of disorders may assist in novel drug development leading to multiple disease management and re-purposing of existing drugs. The polygenic risk score could select super-controls, high risk individuals, rare variants in clinical trials. The sexually transmitted neurodevelopmental traits could be utilized in pre-marital counselling and pre-natal child care. The role of epigenetic factors involving histone methylation, modification in amino acid content imposes higher order control along with dubious environmental component. The criss-cross inheritance of X-chromosome regulates gene expression in male offspring and a single holandric gene was identified to be related to autism. Gene-mining data could lead to biomarker development, early disease detection, prognosis, control and management of psychological and neurodevelopmental disorders.

**Key words:** Psychological/neurodevelopmental disorder, Pleiotropy, Polygenic, Drug-development, disease management, Genome wide association study (GWAS).

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## INTRODUCTION

In the post-genomic epoch, the application of molecular signature in disease studies is taking a pivotal role in health and medical sciences. In case of complex traits, the hunting for causal genes and development of a corresponding network is essential to develop innovative ensemble decision approaches in disease tracing and management.[1] The identification of molecular signature from omics data could be applied for disease-specific-diagnostics and accurate phenotypic classification of samples. The Omic database includes high throughput measurement technologies for biomolecules such as DNA, RNA and proteins and are referred to as genomics, transcriptomics, proteomics and metabolomics. In selection of molecular signature though financial cost, technical practicality, robustness of selected method and fidelity of the system are crucial but if all else is equal, a signature that could be measured via PCR or Western Blot could be favoured over other technique that involve many more protocol steps as well as biohazards.[2] The human genome comprises 6 billion nucleotides of DNA packed into two sets of 23 chromosomes, one set inherited from each parent. The probability of obtaining polymorphism in human DNA is high due to the relatively large size of the genome. Genomic variability at DNA level can occur in forms including single nucleotide polymorphism (SNP), variable number of tandem repeat (VNTR), transposable element, structural aberration, copy

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number variation (CNV) and extra-chromosomal variation. The development and use of DNA-based markers and their application in the health and medicine sector to study genetic variation is regarded as the most significant and effective additional resource with high heritability.[3]

## OBJECTIVES

In India genetic studies in the health care sector is standing at the stage of infancy. Though a well-driven genetic study could aid in the management of psychological health of affected persons and enhance social productivity. In Indian social scenario the ethical and confidentiality parameter limits the direct sharing as well as utilization of clinical information. The genetic data resource is also not enough for a vivid study. In such a context, the judicious application of the current psycho-genetic information and adjoining assistance of bioinformatics tool could help in the novel drug identification, administering of one drug in multiple diseases, sex-related psycho-trait management, pre-marital, pre-natal counselling, and adult neuro-health management. The genetic control of diseases and adjoining gene ontogeny study could unfold emergence of precise and critical avenues in mental health sector. In this paper an attempt is executed to emphasise the applicability of gene-mining in psychological and neurodevelopmental disorders to inventorize novel way to manage mental health sector.

## METHODOLOGY

The method included data mining of journal papers and gene databank search. The method included three segments. In the first segment of study web-mining approach was taken using simple Boolean strings in Google Scholar platform. Journal papers were searched for gene card + drug development + psychological disorders + human and obtained 3130 search results. Out of all papers 50 papers were found relevant to the study objective. These papers were kept in a single folder. The abstract of all the papers were read and 10 papers were selected. In a similar way a search involving polygenic risk score + gene card + drug repurposing + psychological disorders + human gave 34 papers. Another search gave 22 result with a string of pleiotropy + gene card + drug repurposing + psychological disorders + human. Out of these selected 66 papers further screening was done and 57 best-fit papers were completely examined and the knowledge was used for second segment.

The second segment included the identification of most suitable genes related to psychological disorders and their association with diverse mental disorders were analysed by analysis of 57 screened papers. The detailed ontogenic studies of 52 psychotic genes were presented in separate tables. NCBI BLAST method, DDJB, EMBL database and GENECARDS were searched for obtaining gene ID for advance studies. The data on complete coding sequence (CDS) was obtained for the selected biomarkers with chromosomal position from BLASTn public domain.

The third segment included the identification of only pleiotropic genes for novel drug development and drug repurposing study. Out of 52 genes, 16 genes were found pluripotent and their genetic details were thoroughly investigated for management of neuro-psychological disorders.

## MENTAL HEALTH SCENARIO IN INDIA

In developing countries, much of the mental health care spending is reported to be out of pocket. Individuals purchase modern and traditional treatments if they can afford to do so. A large private health sector exists in low-income countries,[4] with variable quality and cost of treatment. Unregulated markets fail in health sector they fail even more in mental health care. It is unlikely that a country will be able to rely on an unregulated private sector to deliver services that will reduce the burden of mental disorders. In addition to being a large and growing component of disease burden, neuro-psychiatric disorders meet virtually all the criteria by which we determine the need for involvement of genetic knowledge in early diagnosis, detection, prognosis and personalised treatment.[5] These illnesses affect the poor, cause externalities, and inflict catastrophic costs, reduces population productivity and ensures disability.[6]

The alterations in gene expression are implicated in the pathogenesis of several neuropsychiatric disorders, including drug addiction and depression. In India the development of transgenic neuropsychiatric animal models is rare. Biomarkers in neuropsychiatric disorders could yield promising result in the early diagnosis of the disorders. Most of the disorders are complex polygenic traits with a component involving gene-environment interactions. DNA instability, oxidative stress sometime plays evil role and complicates clinical trial. Additionally, comprehensive understanding of chromatin biology is necessary to better appreciate its role in a wide range of neurodevelopmental disorders.[7] The epigenetic regulatory machinery includes DNA methylation and

histone acetylation/deacetylation. These events have an impact on the coordinated expression of multiple genes. There has been an interesting finding about the use of HDAC inhibitors to activate the expression of mRNAs that are down regulated in various neuropsychiatric disorder.[8]

In recent years' new ideas were conceptualized for assessing concrete genes with high fidelity for inception and addition of genetic knowledge in neurodevelopmental disease management. PCR based markers with high heritability could aid the clinicians in early detection and confirmation of psychological disorders. Inclusion of low cost PCR based marking could help in Marker-assisted gene pyramiding (MAPG) in developing countries. Gene pyramiding has been proposed and applied to study linkage to disease and by selecting for two or more than two genes at a time[9] in countries like India.

## GENETICS OF PSYCHOLOGICAL AND NEURODEVELOPMENTAL DISORDER

In humans, psychological as well as neurodevelopmental disorders affect more than 37% of the population in any given year, and are a major cause of disability worldwide. They are characterized by high morbidity, high resource utilization and high rate of disability.[10] Therefore, studies of the pathogenesis of psychological disorders are urgently needed. In some diseases multi-site, integrated multi-omic studies have shown great promise in generating deep insight into disease diagnosis, understanding of mechanism, application and progression of predictive markers for tagging the diseases.[11] Multi-omic study includes a system biology approach including DNA and other cellular metabolites and their interaction.[12] It is anticipated that new diagnostic tools and therapeutic strategies could be obtained with current molecular research in the neurodevelopmental health sector.

The major psychiatric disorders with complex genetics are comparable to other common medical disorders such as diabetes and hypertension. For most of these disorders, linkage studies in families with multiple cases have revealed chromosomal areas that contain susceptibility genes. Psychiatric illnesses such as mood disorders or schizophrenia, bipolar disorders are common chronic neurodevelopmental conditions involving alteration in neuronal structure and function. Large-scale genomic studies showed psychiatric disorders are largely influenced by genetic variation.[13] Many risk loci have already been identified through genome-wide association studies (GWAS) for disorders spanning schizophrenia (SCZ), bipolar disorder (BIP), major depressive disorder (MDD), and attention-deficit/hyperactivity disorder (ADHD). Analysis of well-powered GWAS and exome-data studies showed some psychiatric disorders lack specific marker and a genetic variant often influences many neurodevelopmental traits. Widely different chromosomal regions were also found to be associated with some traits. These pleiotropy and polygenic inheritance of most of the psychiatric genes needs a thorough understanding with epigenetic control to comprehend the developmental complexity.[14]

In recent years, genes have begun to be identified for disorders such as schizophrenia (e.g., DISC1, TCF4, ZNF804A),[15] bipolar affective disorder (CACNA1C, ODZ4),[16] autism (neuroligins, neurexins),[17] attention deficit disorder (DAT, DRD4),[18] and alcohol dependence (GABRA2, ADH4).[19] Genetic studies of Alzheimer's disease (APOE) and several forms of neurodevelopmental retardation (Down's syndrome, Fragile X) have already reached an optimum level.[20] Functional studies related to single gene vulnerability factors have been initiated and control of those diseases are comparatively easy. Compilation and stream-lining of accumulated genetic information of majority of psychological disorders could lead to generation of a psychiatome for need based molecular detection and management of neurodevelopmental disorders.

India is standing at an infancy in application of molecular genetics in management of psychological disorders. An initial study to identify all the important psychotic genes and construction of a reliable primary database for each disorder could be a good beginning in neurodevelopmental health sector in developing countries.[21] The candidate gene approach in a metabolic disorders identified gene *PCSK9* with 'knockout' mutation leading to promising results in clinical trials,[22] loss of functional mutation in *SLC30A8*[23] reduced the risk of type 2 diabetes, and loss of functional *LPA* mutation reduce plasma lipoprotein levels and cardiovascular disease risk[24] in human. Candidate gene approach could be efficiently utilized in generation of molecular psychological signature in mental health sectors.

The second step will be the selection and identification of pleiotropic markers from the initial data to discover new drugs for multi-disease resistance or re-purposing of an existing drug in cure of related diseases. The disease score and molecular markers could be correlated using association study to create true molecular signature for each psychological disorder. This study identified 52 genes associated with different types of neurodevelopmental disorders by text-mining approach (Table 1).

**Table 1: Neuro-psyhiatric gene database generated by text-mining approach.**

| Serial No. | Genes and Abbreviation of Genes | Gene responsible for Mental Disorders |
|---|---|---|
| 1 | 5-HTT = 5-hydroxytryptamine transporter | Generalized Anxiety Disorder, Alzheimer's Disease, Clinical Depression, Anxiety Disorder |
| 2 | A beta = amyloid beta-peptide | Alzheimer's Disease |
| 3 | ACT = alpha1-antichymotrypsin | Alzheimer's Disease |
| 4 | ADH2=alcoholdehydrogenase2 | Alcohol Abuse |
| 5 | ALDH2=aldehydededehydrogenase-2 | Alcohol Abuse |
| 6 | APOA4=apolipoproteinA-4 | Autism, Schizophrenia |
| 7 | APOC3=apolipoproteinC3 | Depressive disorder (major)* |
| 8 | APOE=apolipoproteinE | Alzheimer's Disease |
| 9 | ARX=aristaless-relatedhomeobox | Intellectual Disability |
| 10 | BCHE=butyrylcholinesterase | Huntington's chorea |
| 11 | BCL-2=Bcelllymphomaprotein2 | Schizophrenia |
| 12 | BIN1=bridgingintegrator1 | Alzheimer's Disease |
| 13 | CCK=cholecystokinin | Anxiety, Panic, Hallucination |
| 14 | CHI3L1=chitinase3-like1 | Alzheimer's Disease |
| 15 | CHRNA5=cholinergicreceptornicotinicalpha 5 | Substance Abuse |
| 16 | CHRNB4 = cholinergic receptor nicotinic Beta 4 | ADHD, Smoking* |
| 17 | COMT = catechol-O-methyl transferase | Alcohol Abuse |
| 18 | CYTH4 = cytohesin 4 | Schizophrenia, Bipolar |
| 19 | DRD2 = dopamine receptor D2 | Schizophrenia, Parkinsonism |
| 20 | DRD4 = dopamine D4 receptor | Schizophrenia, Bipolar Disorder, Parkinsonism, Attention Deficit Hyperactivity Disorder |
| 21 | GRIK2 = glutamate receptor ionotropic kainate 2 | Alzheimer's Disease |
| 22 | GRIN1 = G proteinregulated inducer of neurite outgrowth 1 | Neurodevelopmental Disorder |
| 23 | GRN = growth factor progranulin | Dementia |
| 24 | HERP = homocysteine-induced endoplasmic reticulum protein | Parkinsons, Alzheimer's Disease |
| 25 | HOPA=humanoppositepaired-containing | Depression, Phobia |
| 26 | IL-10=Interleukin-10 | Schizophrenia, Depression |
| 27 | IL-6=interleukin-6 | Depression, Alzheimer's Disease |
| 28 | LBP-1c=Upstream-bindingprotein1c | Alzheimer's Disease |
| 29 | MAOA=monoamineoxidase-A | Autism Spectrum Disorder, Alzheimer's Disease, Manic Depressive Disorder, Panic Disorder |
| 30 | MAOB=monoamineoxidaseB | Alzheimer's Disease, Parkinsonism, Depression |
| 31 | MAPT=microtubuleassociated-proteintau | Alzheimer's Disease, Dementia |
| 32 | MECP2=methylCpG-binding protein 2 | Autism Spectrum Disorder |
| 33 | MHC = major histocompatibility complex | |
| 34 | NF1 = neurofibromatosis type 1 | Attention Deficit Hyperactivity Disorder |
| 35 | NOS1 = Nitric Oxide Synthase | Schizophrenia, Bipolar Disorder |
| 36 | NR2B = NMDA receptor 2B | Autism Spectrum Disorder |
| 37 | NRXN1 = Neurexin-1 | Autism Spectrum Disorder |
| 38 | TP53 = Tumour suppressor protein 53 | Schizophrenia |
| 39 | PDYN = prodynorphin | Substance Abuse |
| 40 | PRNP = prion protein | Neurogeneretive disorder |
| 41 | PSEN1 = presenilin 1 | Alzheimer's Disease |
| 42 | RELN=Reelin | Schizophrenia, Bipolar Disorder, Autism Spectrum Disorder |

Continued...

**Table 1: Cont'd.**

| Serial No. | Genes and Abbreviation of Genes | Gene responsible for Mental Disorders |
|---|---|---|
| 43 | RPL10 = ribosomal protein L10 | Autism Spectrum Disorder and Intellectual Disability |
| 44 | SLC6A2 = solute carrier family 6 (neurotransmitter transporter, serotonin) member 2 | Anxiety |
| 45 | SLC6A3 = solute carrier family 6 (neurotransmitter transporter, serotonin) member 3 | Attention Deficit Hyperactivity Disorder, Autism Spectrum Disorder, Parkinsonism |
| 46 | SLC6A4 = solute carrier family 6 (neurotransmitter transporter, serotonin) member 4 | Obsessive Compulsive Disorder, Generalized Anxiety Disorder, Clinical Depression |
| 47 | SORL1 = sortilin-related receptor 1 | Alzheimer's Disease |
| 48 | SPRY3 = Sprouty Homolog 3 | |
| 49 | TDP-43 = transactiveresponse DNA-binding protein of 43ku | Alzheimer's Disease |
| 50 | TH= tyrosine hydroxylase | Bipolar Disorder |
| 51 | TNFalpha = tumor necrosis factor alpha | Alzheimer's Disease, Depression, Parkinsonism |
| 52 | YY1= Yin Yang 1 | Neurodevelopmental Disorder |

*US20120178118A1 - Biomarkers for monitoring treatment of neuropsychiatric diseases

The genes are located in 19 autosomes of haploid chromosome set and involves both the sex chromosomes. The details of the monogenic, polygenic and pleiotropic inheritance pattern of identified genes could be effectively applied for treatment of psychiatric diseases. The endogenous and exogenous environment also plays a pivotal role in occurrence of different traits. The details of all the genes along with ontogeny were tabulated in Table 2. The ontogenic details of the protein coding sequence (CDS) information could be used for construction of robust primers for early detection of diseases. Apart from chromosome 8, 10, 13 and 23 all other chromosomes harbour different genes related to various psychological disorders.

Seven genes were detected in X chromosome and chromosome 11 and 17 harbour 6 genes each. X-chromosome is very crucial in control of psychotic traits and in male offspring as it comes directly from the mother, the genetic architecture of mother plays a pivotal role in regulation of neurodevelopmental health scenario of male offspring. Five psychotic loci are present in chromosome 12. The male bias in autism prevalence remained a debatable mystery with disability of autosomal genes to fully explain the disorder. The conglomeration of known DNA susceptibility variants with major sex-linked gene explained the mystery.[25] SPRY3 is the only holandric gene involved in autism spectrum disorder. An annotated region on chromosome Yq12 ~60 kb from *SPRY3* acts as a silencer of Y-linked *SPRY3* expression. Deletion of a β-satellite repeat, or alterations in chromatin structure in this region due to transacting factors, could affect the proposed silencing function, leading to reactivation and inappropriate expression of Y-linked *SPRY3* gene.[26] The study revealed a major segment of sex-related neurodevelopmental disorder in male offspring is being inherited from mother in criss-cross fashion (Table 3).

Additionally, 17 psychological disorders were found to be polygenic in nature. Five disorders showed monogenic control. The association of 17 genes were noticed with Alzheimer's disease and nine genes with schizophrenia. Autism shows association with eight genes. Depression and Parkinsonism shows association with six genes. Five loci are associated with bipolar disorder. Attention deficit hypersensitivity disorder showed tetra-genic control. Trigenic influence is noticed in neurodevelopmental disorders and alcohol abuse. Digenic control is detected in generalized anxiety, anxiety, clinical depression, major depressive disorder, intellectual disability, panic, substance abuse and dementia. The highly polygenic nature of three disease traits including Alzheimer's, schizophrenia and autism shows more environmental influence. The complex gene regulation in these diseases were revealed by detailed statistical analysis of the patient's genomic architecture involving genomic structural equation modelling leading to multivariate genetic analysis of complex traits.[27]

A study involving additive logistic regression analysis identified a huge number of SNPs in all data sets of the human genome and summary statistics revealed the association among 8 disorders using pairwise genetic correlation and linkage disequilibrium score in regression analyses.[28] Among 146 lead SNPs 109 were pleiotropic. Of the 109 pleiotropic loci, 83% and 72% are associated with Schizophrenia and bipolar

**Table 2: Gene ontogeny of 52 genes associated with PSYCHOLOGICAL AND NEURODEVELOPMENTAL psychological disorders.**

| Gene | Chromosome | Nature/Type | Official Full Name | Gene ID |
|---|---|---|---|---|
| 5-HTT | Chromosome 17, NC_000017.11 (30194319..30235697, complement) | Protein Coding | 5-hydroxytryptamine transporter | 6532 |
| A beta | Chromosome 21, NC_000021.9 (25880550..26171128, complement) | Protein Coding | amyloid beta-peptide | 351 |
| ACT | Chromosome 14, NC_000014.9 (94612391..94624053) | Protein Coding | alpha1-antichymotrypsin | 12 |
| ADH2 | Chromosome 4, NC_000004.12 (99304971..99321401, complement) | Protein Coding | alcoholdehydrogenase2 | 125 |
| ALDH2 | Chromosome 12, NC_000012.12 (111766933..111817532) | Protein Coding | aldehydedehydrogenase-2 | 217 |
| APOA4 | Chromosome 11, NC_000011.10 (116820700..116823304, complement) | Protein Coding | apolipoproteinA-4 | 337 |
| APOC3 | Chromosome 11, NC_000011.10 (116829907..116833072) | Protein Coding | apolipoproteinC3 | 345 |
| APOE | Chromosome 19, NC_000019.10 (44905796..44909395) | Protein Coding | apolipoproteinE | 348 |
| ARX | Chromosome X, NC_000023.11 (25003694..25015965, complement) | Protein Coding | aristaless-relatedhomeobox | 170302 |
| BCHE | Chromosome 3, NC_000003.12 (165772904..165837423, complement) | Protein Coding | Butyrylcholinesterase | 590 |
| BCL-2 | Chromosome 18, NC_000018.10 (63123346..63320280, complement) | Protein Coding | Bcelllymphomaprotein2 | 596 |
| BIN1 | Chromosome 2, NC_000002.12 (127048023..127107154, complement) | Protein Coding | bridgingintegrator1 | 274 |
| CCK | Chromosome 3, NC_000003.12 (42257824..42266185, complement) | Protein Coding | Cholecystokinin | 885 |
| CHI3L1= | Chromosome 1, NC_000001.11 (203178931..203186704, complement) | Protein Coding | chitinase3-like1 | 1116 |
| CHRNA5 | Chromosome 15, NC_000015.10 (78565520..78595269) | Protein Coding | cholinergicreceptornicotinicalpha 5 | 1138 |
| CHRNB4 | Chromosome 15, NC_000015.10 (78623282..78655586, complement) | Protein Coding | cholinergic receptor nicotinic Beta 4 | 1143 |
| COMT | Chromosome 22, NC_000022.11 (19941772..19969975) | Protein Coding | catechol-O-methyl transferase | 1312 |
| CYTH4 | Chromosome 22, NC_000022.11 (37282508..37315341) | Protein Coding | cytohesin 4 | 27128 |
| DRD2 | Chromosome 11, NC_000011.10 (113409595..113475398, complement) | Protein Coding | dopamine receptor D2 | 1813 |
| DRD4 | Chromosome 11, NC_000011.10 (637269..640706) | Protein Coding | dopamine D4 receptor | 1815 |
| GRIK2 | Chromosome 6, NC_000006.12 (101393708..102070083) | Protein Coding | glutamate receptor ionotropic kainate 2 | 2898 |
| GRIN1 | Chromosome 9, NC_000009.12 (137139092..137168759) | Protein Coding | G proteinregulated inducer of neurite outgrowth 1 | 2902 |
| GRN | Chromosome 17, NC_000017.11 (44345302..44353106) | Protein Coding | growth factor progranulin | 2896 |
| HERPUD | Chromosome 16, NC_000016.10 (56932142..56944864) | Protein Coding | homocysteine-induced endoplasmic reticulum protein | 9709 |
| HOPA | Chromosome X, NC_000023.11 (71118596..71142450) | Protein Coding | humanoppositepaired-containing | 9968 |
| IL-10 | Chromosome 1, NC_000001.11 (206767602..206772494, complement) | Protein Coding | Interleukin-10 | 3586 |
| IL-6 | Chromosome 7, NC_000007.14 (22725889..22732002) | Protein Coding | interleukin-6 | 3569 |

**Table 2: Cont'd.**

| Gene | Chromosome | Nature/Type | Official Full Name | Gene ID |
|---|---|---|---|---|
| LBP-1c | Chromosome 12, NC_000012.12 (51093656..51173135, complement) | Protein Coding | leader-bindingprotein1c | 7024 |
| MAOA | Chromosome X, NC_000023.11 (43654907..43746824) | Protein Coding | monoamineoxidase-A | 4128 |
| MAOB | Chromosome X, NC_000023.11 (43766610..43882450, complement) | Protein Coding | monoamineoxidaseB | 4129 |
| MAPT | Chromosome 17, NC_000017.11 (45894382..46028334) | Protein Coding | microtubuleassociated-proteintau | 4137 |
| MECP2 | Chromosome X, NC_000023.11 (154021573..154097731, complement) | Protein Coding | methylCpG-binding protein 2 | 4204 |
| MHC(HLA-C) | Chromosome 6, NC_000006.12 (31268749..31272092, complement) | Protein Coding | major histocompatibility complex | 3107 |
| NF1 | Chromosome 17, NC_000017.11 (31094927..31377677) | Protein Coding | neurofibromatosis type 1 | 4763 |
| NOS1 | Chromosome 12, NC_000012.12 (117208142..117361802, complement) | Protein Coding | Nitric Oxide Synthase | 4842 |
| NR2B | Chromosome 12, NC_000012.12 (13537337..13982012, complement) | Protein Coding | NMDA receptor 2B | 2904 |
| NRXN1 | Chromosome 2, NC_000002.12 (49918503..51032536, complement) | Protein Coding | Neurexin-1 | 9378 |
| P53 | Chromosome 17, NC_000017.11 (7668402..7687550, complement) | Protein Coding | protein 53 | 7157 |
| PDYN | Chromosome 20, NC_000020.11 (1978756..1994285, complement) | Protein Coding | Prodynorphin | 5173 |
| PRNP | Chromosome 20, NC_000020.11 (4686456..4701588) | Protein Coding | prion protein | 5621 |
| PSEN1 | Chromosome 14, NC_000014.9 (73136436..73223691) | Protein Coding | presenilin 1 | 5663 |
| RELN | Chromosome 7, NC_000007.14 (103471784..103989658, complement | Protein Coding | Reelin | 5649 |
| RPL1 | Chromosome X, NC_000023.11 (154398065..154402339) | Protein Coding | ribosomal protein L10 | 6134 |
| SLC6A2 | Chromosome 16, NC_000016.10 (55655928..55706192) | Protein Coding | solute carrier family 6 (neurotransmitter transporter, serotonin) member 2 | 6530 |
| SLC6A3 | Chromosome 5, NC_000005.10 (1392794..1445440, complement) | Protein Coding | solute carrier family 6 (neurotransmitter transporter, serotonin) member 3 | 6531 |
| SLC6A4 | Chromosome 17, NC_000017.11 (30194319..30235697, complement) | Protein coding | solute carrier family 6 (neurotransmitter transporter, serotonin) member 4 | 6532 |
| SORL1 | Chromosome 11, NC_000011.10 (121452314..121633763) | Protein Coding | sortilin-related receptor 1 | 6653 |
| SPRY3 | Chromosome X, NC_000023.11 (155612565..155782459); Chromosome Y, NC_000024.10 (56954255..56968979) | Protein Coding | Sprouty Homolog 3 | 10251 |
| TDP-43 | Chromosome 1, NC_000001.11 (11012654..11030528) | Protein Coding | transactiveresponse DNA-binding protein of 43ku | 23435 |
| TH | Chromosome 11, NC_000011.10 (2163929..2174081, complement) | Protein Coding | tyrosine hydroxylase | 7054 |
| TNF-alpha | Chromosome 6, NC_000006.12 (31575565..31578336) | Protein Coding | tumor necrosis factor alpha | 7124 |
| YY1 | Chromosome 12, NC_000078.6 (108792945..108820148) | Protein Coding | Yin Yang 1 | 22632 |

*Nature/Type-Protein Coding

**Table 3: Location of all the Identified Genes with Chromosomal Position with Pleiotropic Contribution.**

| Chromosome | Specific Genes | Total Gene |
|---|---|---|
| 1 | TDP43, CHI3LI, ILIO | 3 |
| 2 | BINI, NRXNI | 2 |
| 3 | BCHE, CCK, | 2 |
| 4 | ADH2 | 1 |
| 5 | SLC6A3 | 1 |
| 6 | GRIK2, MHC (HI.AC), TNF-ALPHA | 3 |
| 7 | IL-6, RELN | 2 |
| 8 | No gene | 0 |
| 9 | GRINI, | 1 |
| 10 | No gene | 0 |
| 11 | APOA4, APOC3, DRD2, DRD4, SORLI, TH | 6 |
| 12 | ALDH2, LBP-IC, NOSI, NR2B, YYI | 5 |
| 13 | No gene | 0 |
| 14 | PSENI, ACT | 2 |
| 15 | CHRNA5, CHRNB4, | 2 |
| 16 | SLC6A2, HERPUD, | 2 |
| 17 | 5-HTT, GRN, MAPT, NF-1, P53, SLC6A4, | 6 |
| 18 | BCL-2 | 1 |
| 19 | APOE | 1 |
| 20 | PDYN, PRNP | 2 |
| 21 | A-BETA | 1 |
| 22 | COMT, CYTH4, | 2 |
| 23 | No gene | 0 |
| x | ARX, HOPA, MAOA,MAOB, MECP2, RPLI, SPRY3 | 7 |
| y | SPRY3 | 1 |

disorders. 23 pleiotropic loci were identified for four common neurodevelopmental disorders.[29-31] Eleven of the 23 variants were associated with the intron of a protein coding region and 7 additional lead SNPs had at least one protein coding gene within 100kb region in genomic DNA. Our study found 16 genes of pivotal importance in management of mental anomalies (Table 4). Among them 5 were most significant with diverse genetic control. The Netrin-1 receptor gene DCC showed the highest pleiotropic ability controlling eight psychiatric disorders. DCC is the plausible candidate gene guiding axonal growth during neuro-development.[32] Gene expression data indicate that DCC expression peaks during prenatal development.

The second most pleiotropic locus in an intron of RBFOX1 (RNA binding Fox-1 homolog-1) associated with seven disorders except anxiety neurosis (AN).[33] RBFOX1 (previous gene ID A2BP1) encodes a splicing regulator mainly expressed in neurons and known to target several genes important to neuronal developments including NMDA Receptor 1 and voltage gated Calcium channels. A NOX4 downstream loci was related to five disorders Schizophrenia, bipolar, attention deficit disorder, anxiety neurosis and major depressive disorder. NOX family genes codes for subunits of NADPH oxidase.[34] NOX4 is a major source of superoxide production of the human brain and a promoter of neural stem cell growth.[35] BRAF and KDM7A gene shows association with four disorders Schizophrenia, bipolar, attention deficit disorder and oppressive compulsive disorder. BRAF contributes to postsynaptic responses of hippocampal neurons and is a member of MAP kinase signal transduction pathway.[36] KDM7A takes part in nervous system development in the midbrain region. This gene is related to production of an oxygenase protein family with significant role in cytosine-demethylation process. The sequencing of this methyl lysine demethylase will provide information about post-tranlational modification of N-terminus of unstructured tails of histone proteins. Accordingly, reversal of these modifications has important consequences in processes such as gene expression, transcriptional regulation and ultimate genome stability.[37]

## Advantages of application of Gene Pleiotropy

Accumulating evidence suggests that pleiotropy widely exists among different traits, such as psychiatric, metabolic syndrome traits and cancers.[38] In human diseases *PTPN22* locus is associated with multiple auto-immune disorders,[39] such as rheumatoid arthritis, Crohn's disease, and type I diabetes; the *TERT-CLPTM1L* locus associated with bladder, glioma, and lung cancers.[40] A comprehensive update[41] on genomics has provided GWAS results on 8.87 million SNP-phenotype associations in 2082 clinical studies with $p \leq 0.05$. Such a rich data resource allows characterizing the molecular mechanism and greatly widens our understanding of the genetic architecture that underlies complex human phenotypes and accountability of genes in disease manifestation (Table 3).

The insight into biological control of pleiotropic diseases would be more beneficial in clinical practice leading to time bound validation of diagnostic techniques. One instant benefit is the development of more affordable clinical tests, such as blood tests, DNA test, advanced karyotyping accompanying imaging tests for disease diagnosis and accuracy in measurement.

**Table 4: Major Genes related to 8 Psychological and Neuro-developmental Disorders.**

| Gene | Chromosome | Nature/Type | Official Full Name | Gene ID |
|---|---|---|---|---|
| DCC | 18 | Protein coding | Trans-membrane protein | 1630 |
| RBFOXl | 16 | Protein coding | RNA binding motif | 54715 |
| NOX4 | 11 | Protein coding | Catalytic subunit of NADPH complex | 50507 |
| MRPS33 | 7 | Protein coding | Mammalian Mitochondrial Ribosome | 51650 |
| BRAF | 7 | Protein coding | RAF family of Serine-Threonine Kinase | 673 |
| KDM7A | 7 | Protein Coding | Lysine demethylase 7 | 80853 |
| GRIAl | 5 | Protein Coding | Glutamate Ionotropic receptor AMPA type subunit 1 | 2890 |
| GRIN2A | 16 | Protein Coding | Glutamate Ionotropic receptor NMDA type subunit 2A | 2930 |
| GRM3 | 7 | Protein Coding | Glutamate Metabotropic Receptor 3 | 2913 |
| SRR | 17 | Protein Coding | Serine racemase, D-serine lyase | 63826 |
| CAV2 | 7 | Protein Coding | Caveolin2 | 858 |
| CAV3 | 3 | Protein Coding | Caveolin3 | 859 |
| CACNAlC | 19 | Protein Coding | Calcium voltage-gated channel subunit alpha! A | 775 |
| CHRNB3 | 15 | Protein Coding | Cholinergic receptor nicotinic beta 3 subunit | 1143 |
| CHRNB4 | 15 | Protein Coding | Cholinergic receptor nicotinic beta 4 subunit | 1143 |
| CHRNB5 | 15 | Protein Coding | Cholinergic receptor nicotinic beta 5 subunit | 1143 |

Another potential advantage is the discovery of novel drugs for multiple disease treatment.[42] Pleiotropic control of two diseases connected through a common biological mechanism leads to discovery of a single drug with multi-tasking effect. The calcium antagonist drugs have been used for the treatment of hypertension since the 1960s[43] but could be applied in control of several psychiatric diseases due to a mechanistic control on L-type calcium channel subunit of *CACNA1C* gene. *CACNA1C* SNPs were found to have shared effects across attention deficit hyperactivity disorder (ADHD), autism, bipolar, Schizophrenia, autism and major depressive disorder implying that common variation in *CACNA1C* may be associated with particular symptom clusters instead of one particular disorder.[44]

In addition to GWAS findings, large scale exome sequencing studies have shown that rare disruptive mutations within calcium ion channels are enriched in patients with schizophrenia and autism. Furthermore, missense mutations in exon 8, or the alternatively spliced exon 8a, of *CACNA1C* can cause an autosomal dominant genetic disorder named Timothy syndrome (TS) associated with a missense mutation. TS is a multisystem channelopathy characterized by cardiac defects, craniofacial abnormalities, autism, and cognitive impairments. There are 2 common types of TS characterized by mutation; TS1 (G406R in exon 8a) and the more severe form TS2 (G406R or G402S in exon 8). Both TS1 and TS2 are characterized by gain-of-function mutations in *CACNA1C*. Genetic variation in voltage-gated calcium channel genes show association with several other complex multigenic neuropsychiatric disorders such as autism, epilepsy and migraine as well as schizophrenia as well as structural abnormalities.[45]

## Accountability of Polygenic traits

GWAS also revealed the polygenicity at genetic level with small effect of each gene in ultimate disease development.[46] Analysis of 37,000 cases and 113,000 controls identified 108 associated regions related to schizophrenia. The significant genetic variants together only explained 3.4% of the liability scale for schizophrenia, indicating involvement of many more variants. The extent of polygenicity reveals that everyone harbours risk variants, but those affected likely carry a higher, and possibly unique burden of risk factors, which is in accordance with the spectrum of clinical presentations. With 108 regions associated and no immediate knowledge about the functional effects of the majority of the hits in genome necessitates further analysis by increasing sample size in SCZ.[47]

In this decade FDA developed 45 new drugs of which 3 were associated with psychiatry. The challenges in developing novel therapeutics for psychiatric disorders involves etiological heterogeneity, the complex and polygenic nature of genetic risk and the definition of psychiatric disorders based on the range and duration of symptoms (that are subjective, self-reported or observational). The knowledge of polygenic loci may help to identify targets for novel therapeutics or repurposing of existing drugs leading to repositioning. Integration of

genetic data can be used for target selection, matching targets for several disorders allowing a reduction in clinical trial costs such as by accurate identification of high risk individuals.[48,49] Polygenic risk score (PRS) is an approximate measure of individual's common variant in genetic propensity for a given disorder and, at population level shows some predictive power for case-control status. PRS approaches provide several potential routes to drug development, including identification of genetically associated endophenotypes and biomarkers. Clinical trial efficacy could be optimized using PRS. *Super controls* can be chosen by selecting participants with very low PRS for the disease, or PRS for low risk of side-effects or where differential diagnosis is unclear. This may convey particular benefit in trials for diseases such as Alzheimer's, where defined case and control identification is challenging. The PRS distribution could select high risk individuals. This mode amongst other benefits may be cost effective and promising than the sibling design.[50] Rare variants, discovered by large scale sequencing efforts, can also be included in these analyses, particularly the known recurrent Copy Number Variations in Autism and Schizophrenia.[51] These are complemented by high throughput sequencing efforts in these disorders. Although rare mutations are only found in a small percentage of cases with most common disorder, integrative pathway analysis including common and rare variants might increase power to detect statistically significant enriched pathways.[52,53]

The suitability of using phenotypic correlations as a proxy for genetic ones in various traits concludes that while the conjecture may be true in traits with high heritability, particularly those related to growth, there are still exceptions and the conjecture most likely does not apply to all traits in general. Since phenotypic correlation is segmented into additive genetic and environmental effects. The term environment represents any effects that are not additive genetic, differences between phenotypic and genetic correlations must be explained by the relationship between genetic and environmental effects.[54,55] Environmental effects often act in the same direction and through the same pathways as genetic effects, which leads to a similarity between phenotypic and genetic correlations. On the contrary, some scientists suggest that certain traits have environmental effects that act in the opposite direction to the genetic effects, which could reflect the conclusion of who found lower correlation for life history and behavioural traits than morphological ones in disease development.[56,57]

## CONCLUSION

Our study identified a total of 53 genes associated with major psychological disorders. The gene ontogeny information classified the genes into monogenic, oligogenic or polygenic categories. The studies on gene action also revealed pleiotropic and polygenic control of traits. The pleiotropic control mechanism of genes in psychological disorders may assist in novel drug development leading to multiple disease management, early low-cost detection techniques and re-purposing of existing drugs. The polygenic traits could identify selection of super-controls and high risk individuals, rare variants in clinical trials, sample size regulation. The sexually transmitted neurodevelopmental traits could be utilized in pre-marital, pre-natal counselling. The gene-mining data could lead to biomarker development, early disease detection, prognosis, control and holistic management of psychological and neurodevelopmental disorders.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## SUMMARY

The gene mining of available genetic resources could assist in early disease diagnosis, prognosis, pre-marital counselling, family planning, new drug invention and drug re-purposing leading to holistic management of psychological and neurodevelopmental disorders.

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